

**Translation**

**PATENT COOPERATION TREATY**

**PCT**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**  
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>F549PCT</b>	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. <b>PCT/JP2004/005983</b>	International filing date (day/month/year) <b>26.04.2004</b>	Priority date (day/month/year) <b>28.04.2003</b>	
International Patent Classification (IPC) or national classification and IPC			
Applicant <b>SEKISUI CHEMICAL CO., LTD.</b>			

<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <b>10</b> sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> (<i>sent to the applicant and to the International Bureau</i>) a total of <b>3</b> sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> <p>4. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Box No. I Basis of the report</li> <li><input type="checkbox"/> Box No. II Priority</li> <li><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li><input type="checkbox"/> Box No. IV Lack of unity of invention</li> <li><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li><input checked="" type="checkbox"/> Box No. VI Certain documents cited</li> <li><input type="checkbox"/> Box No. VII Certain defects in the international application</li> <li><input type="checkbox"/> Box No. VIII Certain observations on the international application</li> </ul>
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Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP	Authorized officer
Facsimile No.	Telephone No.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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## Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

This report is based on translations from the original language into the following language \_\_\_\_\_, which is the language of a translation furnished for the purposes of:

international search (Rule 12.3 and 23.1(b))  
 publication of the international application (Rule 12.4)  
 international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):

the international application as originally filed/furnished  
 the description:  
 pages 1, 2, 4-28 as originally filed/furnished  
 pages\* 3, 3/1 received by this Authority on 28.02.2005  
 pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

the claims:  
 nos. 4-14 as originally filed/furnished  
 nos.\* \_\_\_\_\_ as amended (together with any statement) under Article 19  
 nos.\* 1 received by this Authority on 28.02.2005  
 nos.\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

the drawings:  
 sheets 1/1 as originally filed/furnished  
 sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_  
 sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3.  The amendments have resulted in the cancellation of:

the description, pages \_\_\_\_\_  
 the claims, nos. 2, 3 \_\_\_\_\_  
 the drawings, sheets/figs \_\_\_\_\_  
 the sequence listing (specify): \_\_\_\_\_  
 any table(s) related to sequence listing (specify): \_\_\_\_\_

4.  This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

the description, pages \_\_\_\_\_  
 the claims, nos. \_\_\_\_\_  
 the drawings, sheets/figs \_\_\_\_\_  
 the sequence listing (specify): \_\_\_\_\_  
 any table(s) related to sequence listing (specify): \_\_\_\_\_

\* If item 4 applies, some or all of those sheets may be marked "superseded."

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## Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application

claims Nos. 14

because:

the said international application, or the said claims Nos. 14 relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claim 14 includes an embodiment relating to methods for treatment of the human body by therapy, and thus this International Searching Authority is not required to carry out international preliminary examination on this subject matter under the provisions of PCT Article 34(4) (a) (i) of the PCT and PCT Rule 67.1(iv).

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_\_\_\_\_ are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for said claims Nos. 14

the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

has not been furnished  
 does not comply with the standard

the computer readable form

has not been furnished  
 does not comply with the standard

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

See Supplemental Box for further details.

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Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
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## 1. Statement

Novelty (N)	Claims <u>1, 4-13</u>	YES
	Claims _____	NO
Inventive step (IS)	Claims _____	YES
	Claims <u>1, 4-13</u>	NO
Industrial applicability (IA)	Claims <u>1, 4-13</u>	YES
	Claims _____	NO

## 2. Citations and explanations (Rule 70.7)

Document 1: JP 61-277628 A (Asahi Chemical Industry Co., Ltd.), 8 December 1986, entire document; claims; page 2, lower left column, 2nd line from the bottom to page 3, upper left column, 2nd line from the bottom; examples  
(Family: none)

Document 2: JP 63-160578 A (Asahi Chemical Industry Co., Ltd.), 4 July 1988, entire document; claims; page 2, lower left column to page 4, lower left column (Family: none)

Document 2: JP 60-120821 A (Asahi Chemical Industry Co., Ltd.), 28 June, 1985, entire document & EP 147689 A2 & JP 60-252423 A & JP 61-85317 A & JP 61-87671 A & JP 61-93121 A & JP 61-93122 A & US 4839290 A

Document 4: WILKINSON, K.A. et al., 'Enhancement of the human T cell response to culture filtrate fractions of *Mycobacterium tuberculosis* by microspheres', J. Immunol. Methods, (2000), Vol. 235, No. (1-2), pages 1 to 9

Document 5: JP 61-100522 A (Toray Industries, Inc.), 19 May 1986, entire document; claims; page 2, lower left column to page 3, upper left

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column; examples (Family: none)

Document 6: JP 63-203623 A (Toray Industries, Inc.), 23 August, 1988, entire document; claims; page 2, lower right column to page 3, lower left column; examples (Family: none)

Document 7: Kazutoshi Yamazaki et al., 'Shushu no Kobunshi Oyobi Hyomen Arasa o Yusuru Zairyo ni Okeru Zen Kecchu no Karyukyu Kyuchaku Kyodo no Kento', Polymer Preprints, Japan, (1991), Vol. 40, No. 7, pages 2230 to 2232

Document 8: Kazuo NIIMURA et al., 'Somen Sakusan Cellulose Beads no Shuyo Eshi Inshi Yuki Sayo', The Japanese Journal of Artificial Organs, 1993, Vol. 22, No. 5, pages 1233 to 1237, entire document, page 1234, left column, III.1, page 1235, left column, 2nd line from the bottom to page 1236, the last line

Document 9: JP 6-209992 A (Sekisui Chemical Co., Ltd.), 2 August 1994, entire document; claim 1; page 3, column 4, paragraph [0016] to page 4, column 5, paragraph [0027] (Family: none)

Document 10: Yasuhito, A. et al., 'The endogenous induction of tumor necrosis factor serum (TNS) for adjuvant postoperative immunotherapy of cancer, -changes in immunological markers of the blood-', Japanese Journal of Surgery, 1990, Vol. 20, No. 1, pages 19 to 26

Document 11: Yoshiki Ryoma, 'Hitokuiteki Koakusei Shuyozai Sonogo no Tenkai OK-432 (Picibanil) Sonogo no Tenkai', Biotherapy, 2000, Vol.

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14, No. 9, pages 877 to 885

Document 12: Fujimoto, T. et al., 'Streptococcal preparation OK-432 is a potent inducer of IL-12 and a T helper cell 1 dominant state.', J. Immunol., 1997, Vol. 158, No. 12, pages 5619 to 5626

(1) Document 1 indicates that a system is constituted by applying OK-432, which is a hemolytic streptococcus, together with a water-insoluble support, and by applying this system to a material such as blood, the activity of immune system cells in the material is heightened, and remarkable anti-cancer activity can be obtained.

Document 1 does not directly disclose remarkable strengthening of the cytokine induction capacity in immune system cells caused by the aforementioned OK-432 which is used in conjunction with a support. However, at the time of filing of this application, it would have been known to a person skilled in the art that a hemolytic streptococcus ingredient such as OK-432 has an effect of increasing cytokine induction such as IFN- $\gamma$  and IL-12 in immune system cells, and that said capacity to increase induction of cytokine production contributes to the treatment of cancer, as described in documents 10 to 12. Therefore a person skilled in the art would be capable of predicting that the remarkable anti-cancer activation of immune system cells offered by the supported-bonded OK-432 disclosed in document 1 would be mainly based on the remarkable increase in cytokine induction in said immune system cells.

In addition, including such an insoluble support-OK-

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432 system in an appropriate container to constitute a device or equipment would merely be common practice to a person skilled in the art without requiring reference to document 1, and this feature is not acknowledged to constitute a particular difference in configuration.

(2) In addition, bonding a compound having a cytokine inducing action and an immune system cell activating effect with a known water-insoluble support, remarkably activating immune system cells in a blood material and using said activated immune system cells in an anti-cancer agent were known techniques at the time of filing of this application, as described in documents 2 to 6, and it would not require any particular creative skill on the part of a person skilled in the art to employ a known cytokine-inducing hemolytic streptococcus typified by the aforementioned OK-432 as a ligand substance used together with a support disclosed in documents 2 to 6. In addition, it would be easy for a person skilled in the art to predict, in the same way as for document 1, that the remarkably activated immune system cells thus obtained are constituted by an increased cytokine induction capacity, and that said strengthening of cytokine induction capacity contributes to a remarkable anti-cancer action.

Other points are the same as described in (1).

(3) Moreover, documents 1 to 6 do not specifically indicate that a support with porous properties is used, but it would naturally be easy for a person skilled in the art to predict that increasing the surface area in a support such as that set forth in documents 1 to 6 would

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result in a corresponding improvement in the effectiveness of contact with a cytokine-inducing compound and/or white blood cells in blood, thereby further increasing the cytokine inducing effect. In fact, it was a widely known technique in common practice at the time of filing of this application to increase the irregularities in the support surface, thereby improving the induced production of cytokine in blood materials and the like which said support surface is made to come into contact with, as set forth in documents 7 to 9. It would therefore be easy for a person skilled in the art to conceive of attempting to employ a known porous support as the water-insoluble support set forth in documents 1 to 6, while expecting an improvement in cytokine induction.

(4) Therefore, the inventions set forth in claims 1 and 4 to 13 do not involve an inventive step in the light of a combination of one of documents 1 to 6 and one of documents 10 to 12, or a combination of one of documents 1 to 6, one of documents 7 to 9, and one of documents 10 to 12.

(5) The embodiments of the description of this application indicate, together with data, that a remarkable improvement in the cytokine-inducing effect is observed when OK-432 is used in conjunction with an insoluble support, compared to when OK-432 is used alone, or when an insoluble support is used alone. However, in light of the facts that

(i) It was widely known at the time of filing of this application that the combined use of OK-432 and an

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insoluble support remarkably activates immune system cells, and

(ii) As described above with regard to documents 10 to 12, the remarkable activation in immune system cells in (i) and a remarkable increase in the cytokine induction capacity by said immune cells are acknowledged to be closely related effects,

the remarkable effect asserted by the applicant is an effect which would merely be obvious to a person skilled in the art and is effectively disclosed in documents 1 to 6 in the light of the disclosures and suggestions of the prior art, or at the very least, could be easily accomplished by a person skilled in the art in the light of the disclosures and suggestions of prior art documents, including documents 1 to 6.

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Box No. VI	Certain documents cited		
1. Certain published documents (Rule 70.10)			
Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 03/37375 A1	08.05.2003	31.10.2002	02.11.2001
2. Non-written disclosures (Rule 70.9)			
Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)	